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Single-Photon Emission Computed Tomography Myocardial Perfusion Imaging and the Risk of Sudden Cardiac Death in Patients With Coronary Disease and Left Ventricular Ejection Fraction >35%

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Objectives The aim of this study was to determine whether single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) is an effective method of risk stratification for sudden cardiac death (SCD) in patients with coronary artery disease (CAD) and left ventricular ejection fraction (LVEF) >35%.

Background Most victims of SCD have an LVEF >35%.

Methods The study population included 4,865 patients with CAD and LVEF >35% who underwent gated SPECT MPI. We used Cox proportional hazard modeling to examine the relationship between patient characteristics and SCD.

Results The median age of the population was 63 years (25th, 75th percentile: 54, 71 years), and the median LVEF was 56% (25th, 75th percentile: 50%, 64%). The median follow-up for all patients was 6.5 years (25th, 75th percentile: 3.6, 9.3 years). During follow-up, there were 161 SCDs (3.3%). After multivariable adjustment, LVEF, the Charlson index, hypertension, smoking, antiarrhythmic drug therapy, and the summed stress score (SSS) were associated with SCD (all $p < 0.05$). For each 3-U increase in the SSS, the hazard ratio for SCD was 1.13 (95% confidence interval: 1.04 to 1.23). The addition of perfusion data to the clinical history and LVEF was associated with increased discrimination for SCD events (c-index 0.728). Risk stratification with a derived SPECT nomogram did not result in statistically significant net reclassification improvement ($p = 0.26$) or integrated discrimination improvement ($p = 0.38$).

Conclusions Among patients with CAD and LVEF >35%, the extent of stress MPI perfusion defects is associated with an increased risk of SCD. Future large prospective studies should address the role of perfusion imaging in the identification of high-risk patients with LVEF >35% who might benefit from ICD implantation. (J Am Coll Cardiol 2010;56:206–14) © 2010 by the American College of Cardiology Foundation

Although our treatment of coronary artery disease (CAD) has improved, and age-adjusted mortality due to cardiovascular disease is declining, over 60% of all cardiovascular death is sudden (1). The implantable cardioverter-defibrillator (ICD) is highly efficacious in the prevention of sudden cardiac death (SCD); however, its utility in clinical practice is dependent upon identifying those patients who are at greatest risk (2,3). Although the left ventricular ejection fraction (LVEF) is the gold standard for the risk stratification of SCD, the majority of SCD victims have preserved left ventricular (LV) systolic function (4,5).

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Given the magnitude of SCD events in patients with an LVEF >35%, there is a great need to identify risk factors in

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this population; unfortunately, little is known about the predictors of SCD in patients with LVEF >35%. The objective of this analysis was to determine whether myocardial perfusion defects, observed via single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI), are associated with the occurrence of SCD in patients with LVEF >35%.

Methods

To identify clinical and SPECT MPI variables associated with SCD in patients with CAD and LVEF >35%, we conducted an observational study of patients in the Duke Databank for Cardiovascular Disease (DDCD). The DDCD includes the past medical history and clinical course of over 81,800 cardiovascular patients in the Duke University Health System. A prospective, longitudinal record is established for each patient with angiographically significant CAD. Finally, an emphasis is placed on annual follow-up, major clinical events, and cause-specific death.

Study population. Between January 1993 and December 2006 we identified 4,865 patients with CAD and LVEF >35% who underwent SPECT stress-rest MPI. All patients had CAD (≥75% stenosis of 1 or more major epicardial coronary arteries) documented by coronary angiography within 180 days of their MPI study. In the event that a patient underwent multiple MPIs, only the most recent study was included in the analysis. Patients with incomplete angiographic data, adult congenital heart disease, primary valvular heart disease, or an ICD were excluded.

Follow-up and outcomes. The primary end point in this analysis was SCD. SCD was adjudicated using the previously validated modified Hinkle-Thaler classification system (6–8) and SCD was strictly defined as death within 1 h of symptom onset, or an unobserved death in which the patient was seen and known to be doing well within 24 h of death. Survivors of aborted SCD or resuscitated cardiac arrest were also considered to have experienced SCD and were included in the primary end point. All deaths that did not meet the criteria for SCD were classified as "non-sudden deaths," including noncardiac deaths. An independent clinical events committee reviewed and classified all deaths without knowledge of the clinical data or MPI results. Follow-up was 96% complete.

Clinical information. Demographic and clinical characteristics were recorded prospectively at the time of coronary angiography (9,10). Prospectively collected variables included: age, sex, race, LVEF, hypertension, diabetes, history of heart failure, New York Heart Association (NYHA) functional classification, CAD severity as reflected by the number of diseased vessels, prior myocardial infarction, prior revascularization, peripheral vascular disease, renal insufficiency (chronic kidney disease stage ≥3; estimated glomerular filtration rate <60 ml/min), smoking history, chronic obstructive pulmonary disease, hyperlipidemia, presence of carotid bruits, ventricular S_3 gallop, and a modified Charlson comorbidity index (11). A history of myocardial infarction and heart failure were removed from the Charlson index and examined independently, given their known associations with SCD. When multiple imaging modalities were used to assess LV function, the following hierarchy of LVEF assessment was used: SPECT (n = 1,678) > echocardiography (n = 477) > ventriculography at cardiac catheterization (n = 2,724). Use of baseline beta-blockers and antiarrhythmic medications were incorporated for adjustment in the multivariable analysis.

Stress testing and SPECT imaging. Patients capable of exercise underwent treadmill stress testing with the Bruce protocol, unless an alternative protocol was requested by the ordering physician. Patients unable to exercise underwent pharmacologic stress testing. The SPECT MPI was performed according to the previously described Duke University nuclear laboratory protocol (12,13). In brief, SPECT images were obtained with multi-head detectors with 30 s/projection at rest and 20 s/projection during stress. The studies were independently interpreted by 3 nuclear cardiologists in our laboratory without attenuation correction. All suboptimal studies were repeated. Either the Cedars Sinai QGS/QPS (Los Angeles, California) or Emory Toolbox software (Atlanta, Georgia) programs were used to determine the gated SPECT LVEF. If the nuclear imaging study could not provide LVEF because of gating problems, LVEF data were obtained from other sources.

The SPECT MPI studies were evaluated independently with relative perfusion recorded in each myocardial segment (0 = no defect, 1 = mild defect, 2 = moderate defect, and 3 = severe defect). A cumulative perfusion score during stress, the summed stress score (SSS), was calculated by adding the perfusion scores in all myocardial segments. Accordingly, the SSS incorporates both fixed and reversible defects and would equal 0 in a normal study. The SSS is an established predictor of cardiovascular outcomes, including myocardial infarction and CV death (14–18). The summed rest score (SRS), which is the sum of the perfusion scores in all segments at rest (fixed defects), and the summed difference score (SDS), which is the sum of the differences between the stress and rest perfusion scores (reversible defects), were also determined for each patient using an identical scoring system.

At the time these data were collected we used a 12-segment model. We have subsequently reported an algorithm for conversion of 12-segment perfusion scores to

Abbreviations and Acronyms

CAD = coronary artery disease
CI = confidence interval
DDCD = Duke Databank for Cardiovascular Disease
HR = hazard ratio
ICD = implantable cardioverter-defibrillator
IDI = integrated discrimination improvement
LV = left ventricle/ventricular
LVEF = left ventricular ejection fraction
MPI = myocardial perfusion imaging
NRI = net reclassification improvement
NYHA = New York Heart Association
SCD = sudden cardiac death
SDS = summed difference score
SPECT = single-photon emission computed tomography
SRS = summed rest score
SSS = summed stress score

17-segment scores, which is highly correlated to visual interpretation by the 17-segment model with nearly identical prognostic information (19).

Statistical analysis. Clinical characteristics were examined according to the primary end point (SCD, nonsudden death, and alive at last contact) with percentages for categorical variables and medians with 25th and 75th percentiles for continuous variables. The occurrence of SCD as a function of time after SPECT imaging was examined with survival analysis methods. To address competing risks, patients who died from causes other than SCD were censored at the time of death. Cox proportional hazards regression modeling was used to identify factors that were independently associated with SCD. Unadjusted Cox proportional hazards SCD models were also generated for all candidate variables, including the baseline characteristics, perfusion indexes, and LVEF. After examining the results of a flexible Cox model-fitting approach involving cubic polynomial spline functions (20), the linearity of the unadjusted relationship between each continuous variable and SCD was assessed. When nonlinear relationships with outcomes were identified, variable transformations were implemented to satisfy this model assumption. Unadjusted models were also examined to explore the relationship between beta-blockers, antiarrhythmic drugs, and SCD.

Significant variables were determined with stepwise selection (and backwards elimination) at $p < 0.05$ from the candidate variable list that included baseline characteristics, nuclear perfusion scores, LVEF, use of beta-blockers, and antiarrhythmic pharmacotherapy. The *c*-index was calculated with Cox survival methods for the final model to evaluate the discriminatory accuracy of the model for the occurrence of SCD. The final SCD model was internally validated with a bootstrap resampling technique. One hundred samples were drawn at random with replacement. A model *c*-index was derived for each sample, and mean *c*-indexes with 95% confidence intervals (CIs) were calculated. The variable selection process was applied to each sample, and the number of times significant variables stayed in the final model were reported. Formal risk reclassification analyses were conducted with both the net reclassification improvement (NRI) and integrated discrimination improvement (IDI) methods (21).

All tests were 2-tailed, and statistical significance was declared at alpha <0.05. All analyses were performed with SAS software version 8.2 (SAS Institute, Cary, North Carolina). The study protocol was reviewed and approved by the Duke University Medical Center Institutional Review Board.

Results

Outcomes. The median follow-up for all patients was 6.5 years (25th, 75th percentile: 3.6, 9.3 years). Among 4,865 patients with CAD and an LVEF >35%, 161 (3.3%) patients died suddenly (77 [48%] witnessed, 60 [37%] unobserved, and 24 [15%] after resuscitation). The median time to SCD was 3.0 years (25th, 75th percentile: 1.3, 6.2 years). There were 1,557 (32%) deaths other than SCD. Of the 1,557 deaths other than SCD, 789 were cardiac deaths. The median follow-up in those patients alive at last contact was 7.2 years (25th, 75th percentile: 4.9, 10.2 years).

Patient characteristics. The baseline characteristics are detailed in Table 1. Most of the cohort was male (67%), and 16% were black or African American. The median age of those patients with SCD was 62 years. Although we included patients with an LVEF >35%, among those with SCD, the median LVEF was 51%, and the vast majority of patients had preserved LV function (25th, 75th percentile: 43, 60). The distribution of the LVEF, Charlson comorbidity index, and

Table 1 Baseline Characteristics

Characteristic	SCD (n = 161)	Death Other Than SCD (n = 1,557)	Alive at Last Contact (n = 3,147)
Age, yrs	62 (54–72)	68 (60–74)	60 (52–69)
Male	68.9	62.2	69.0
Black/African American	20.5	16.4	15.9
EF	51 (43–60)	55 (47–63)	57 (51–65)
Summed stress score	8 (4–13)	6 (2–11)	5 (2–10)
Summed rest score	4 (0–8)	2 (0–6)	1 (0–5)
Summed difference score	3 (0–6)	2 (0–5)	2 (0–5)
Hypertension	78.3	73.0	66.1
Diabetes	40.4	39.8	26.6
Heart failure severity			
No heart failure	77.6	75.1	89.6
NYHA functional class I	5.0	4.5	1.5
NYHA functional class II	5.6	6.7	4.4
NYHA functional class III	6.8	8.2	3.3
NYHA functional class IV	5.0	5.5	1.2
CAD severity			
1-vessel disease	27.3	29.6	40.8
2-vessel disease	31.7	25.7	27.2
3-vessel disease	41.0	44.7	32.0
Medical history			
Prior PCI	30.4	30.9	37.3
Prior CABG	36.6	35.8	28.4
Prior myocardial infarction	47.8	45.8	39.2
Cerebrovascular disease	20.5	19.7	10.3
Peripheral vascular disease	23.6	20.6	10.1
Renal insufficiency	5.6	4.8	1.4
Smoking history	72.0	64.8	59.6
Chronic obstructive pulmonary disease	11.8	14.8	5.5
Hyperlipidemia	67.7	60.3	68.4
Charlson comorbidity (≥2)	33.5	35.3	15.8
Physical examination			
Carotid bruits	19.4	20.8	8.4
S_3 gallop	2.5	2.4	1.1
Medications			
Aspirin	61.5	62.1	61.2
ACE inhibitor	39.1	42.1	45.1
Beta-blocker	41.7	47.4	45.4
Antiarrhythmic	6.0	3.5	2.3

Data shown are median (interquartile range) or %.

ACE = angiotensin-converting enzyme; CABG = coronary artery bypass grafting; CAD = coronary artery disease; EF = ejection fraction; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; SCD = sudden cardiac death.

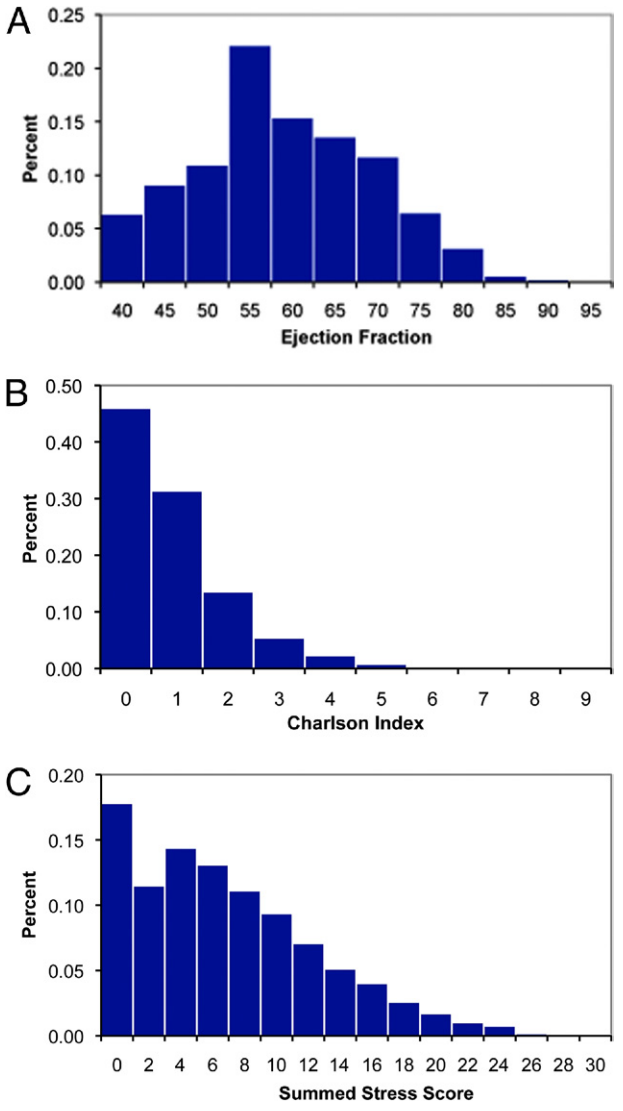

Figure 1 **Distribution of Baseline Left Ventricular Function, Degree of Comorbid Illness, and Stress Perfusion Scores**

Histograms depicting the distribution of **(A)** left ventricular ejection fraction, **(B)** Charlson index, and **(C)** summed stress scores in the study population.

SSS in the study population are shown in Figure 1. Furthermore, <1 in 4 patients with SCD had a diagnosis of heart failure. The median SSS was greatest, 8 (25th, 75th percentile: 4, 13), in those patients with SCD, compared with 6 (25th, 75th percentile: 2, 11) in those who experienced death other than SCD, and 5 (25th, 75th percentile: 2, 10) in those patients alive at last contact. Forty-eight percent of the SCD patients had a prior MI, and 55% had prior revascularization. Among all patients, 2,538 patients (52%) had SPECT before coronary angiography, of which 1,713 had subsequent revascularization. A total of 644 patients (13.2%) underwent SPECT within 60 days of an MI.

Unadjusted time-to-event analyses. We examined the factors associated with SCD in unadjusted Cox models (Table 2). In this cohort with LVEF >35%, age, sex, and prior MI were not associated with the occurrence of SCD. The presence of hypertension, higher NYHA functional classification, CAD severity, cerebrovascular disease, peripheral vascular disease, smoking, diabetes, renal disease, and declining LVEF were all associated with an increased hazard of SCD. Additionally, the presence of comorbid medical illness (as reflected by the Charlson index) was also associated with an increased risk of SCD. In terms of therapeutic history, beta-blocker use at baseline and prior coronary revascularization were not associated with statistically significant reductions in the occurrence of SCD. Antiarrhythmic (Vaughan-Williams class I and III) drug therapy was associated with an increased hazard of SCD. In terms of MPI perfusion scores, every 3-U increase in the SSS was associated with a 23% increase in the hazard for SCD. As shown in Figure 2, patients with an SSS ≥8 had a higher cumulative incidence of SCD when compared with those patients with an SSS <8 (log-rank $p < 0.0001$).

Adjusted analyses of survival free from SCD. After adjustment for clinical characteristics, severity of CAD, and baseline

Table 2 **Unadjusted Factors Associated With SCD**

Variable Name	Likelihood Ratio Chi-Square	HR (95% CI)	p Value
Age	0.77	1.01 (0.99–1.02)	0.3817
Black	3.14	1.43 (0.98–2.10)	0.0766
Male	0.02	1.03 (0.74–1.43)	0.8776
Hypertension	10.88	1.82 (1.25–2.65)	0.0010
NYHA CHF severity class	9.50	1.25 (1.10–1.43)	0.0021
CAD severity (number of diseased vessels)	5.69	1.25 (1.04–1.50)	0.0170
History of MI	0.70	1.14 (0.84–1.56)	0.4016
History of cerebrovascular disease	6.93	1.72 (1.17–2.52)	0.0085
History of peripheral vascular disease	11.85	1.98 (1.37–2.84)	0.0006
Smoker	4.56	1.44 (1.02–2.04)	0.0328
Renal insufficiency	9.58	3.56 (1.81–6.99)	0.0020
Body mass index	1.58	1.02 (0.99–1.04)	0.2094
History of diabetes	10.24	1.69 (1.24–2.32)	0.0014
Charlson index	24.62	1.35 (1.21–1.49)	<0.0001
Carotid bruits	7.09	1.76 (1.19–2.61)	0.0078
COPD	3.22	1.59 (0.99–2.59)	0.0729
Hyperlipidemia	0.09	1.05 (0.76–1.46)	0.7620
History of angina	0.71	0.82 (0.52–1.29)	0.3994
EF (HR per 5%)	39.67	0.78 (0.72–0.85)	<0.0001
Third heart sound	1.09	1.78 (0.66–4.81)	0.2961
Beta-blocker use	2.10	0.79 (0.57–1.09)	0.1469
Antiarrhythmic drug use	5.97	2.62 (1.33–5.14)	0.0145
Summed stress score (HR per 3 U)	26.46	1.23 (1.14–1.32)	<0.0001
Summed rest score (HR per 3 U)	23.59	1.25 (1.15–1.36)	<0.0001
Summed difference score (HR per 3 U)	1.50	1.08 (0.96–1.21)	0.2110
Prior revascularization	0.18	0.94 (0.69–1.28)	0.6749
History of PCI	3.21	0.74 (0.53–1.04)	0.0734

CHF = congestive heart failure; CI = confidence interval; COPD = chronic obstructive pulmonary disease; HR = hazard ratio; MI = myocardial infarction; other abbreviations as in Table 1.

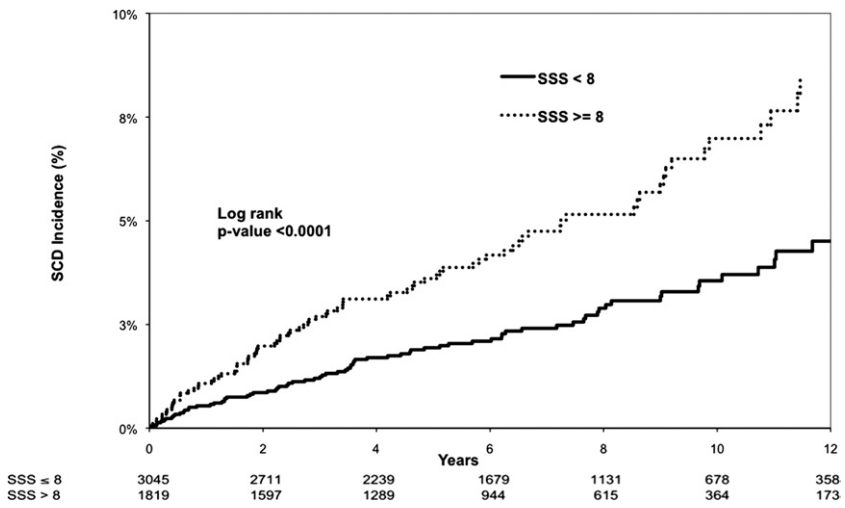

Figure 2 Cumulative Incidence of SCD According to SSS

The incidence of sudden cardiac death (SCD) was greater in those patients with a summed stress score (SSS) of 8 or more versus an SSS <8 (log rank p < 0.0001). The numbers at risk in each group are shown **beneath the x-axis.**

beta-blocker use, Cox proportional hazards modeling identified the Charlson index (hazard ratio [HR]: 1.33, 95% CI: 1.19 to 1.49, p < 0.0001), hypertension (HR: 1.71, 95% CI: 1.17 to 2.50, p = 0.006), antiarrhythmic drug therapy (HR: 2.04, 95% CI: 1.04 to 4.01, p = 0.039), and smoking (HR: 1.42, 95% CI: 1.01 to 2.01, p = 0.047) as factors associated with an increased hazard of SCD (Table 3). Higher LVEF was associated with decreased risk of SCD (HR: 0.74 per 5%, 95% CI: 0.66 to 0.83, p < 0.0001). In terms of MPI, a 3-U increase in the SSS was associated with an increased risk of SCD (HR: 1.13, 95% CI: 1.04 to 1.23, p = 0.004).

To assess the possible influence of revascularization (despite adjustment), we conducted a sensitivity analysis restricted to those patients without post-SPECT revascularization. After excluding patients with subsequent revascularization (n = 1,713), the SSS remained the perfusion index most closely associated with SCD (HR: 1.12 per 3-U increase, 95% CI: 1.01 to 1.24, p = 0.034).

Table 3 Significant Multivariable Predictors of SCD in Patients With CAD and LVEF >35%

Variable	Likelihood Ratio Chi-Square	HR (95% CI)	p Value
LVEF (HR per 5% <58%)*	27.08	0.74 (0.66–0.83)	<0.0001
Charlson index	24.10	1.33 (1.19–1.49)	<0.0001
Summed stress score (HR per 3 U)	8.28	1.13 (1.04–1.23)	0.004
Hypertension	7.59	1.71 (1.17–2.50)	0.006
Antiarrhythmic drug treatment	4.24	2.04 (1.04–4.01)	0.039
Smoker	3.96	1.42 (1.01–2.01)	0.047

*To satisfy linearity assumption, left ventricular ejection fraction (LVEF) values >58 were set to 58. *c*-statistic = 0.728.
Abbreviations as in Tables 1 and 2.

We also sought to determine whether the SSS provided incremental predictive power, when compared with the LVEF, for the occurrence of SCD. With Cox proportional hazards modeling, the addition of the SSS to the clinical history and LVEF led to improvement in the predictive power of the model as reflected by the global chi-square increment (global chi-square increased from 90 to 98 [p for difference = 0.005]; *c*-index 0.710 to 0.728). After inclusion of the nuclear perfusion data, the *c*-index for the overall model improved by 0.018 (95% CI: 0.002 to 0.034). With respect to the final model, on the basis of global likelihood ratio chi-squares, SSS accounted for 27% of the total prognostic information, whereas LVEF accounted for 52%.

Alternative causes of death. We also examined the association between the SSS and alternative outcomes in univariate Cox models. The incremental hazard observed with the SSS was greatest for SCD (Table 4) and exceeded that observed for all-cause death (HR for SCD: 1.23, 95% CI: 1.14 to 1.32, vs. HR for all-cause death: 1.09, 95% CI: 1.06 to 1.12). The SSS was not retained in the stepwise selection process for the final multivariable model for nonsudden death and all-cause mortality.

Bootstrap validation. To assess the validity and stability of our predictive model we conducted serial bootstrap analyses. In

Table 4 Unadjusted HRs/3-U Change in the Summed Stress Score for Different Outcomes

Outcome	HR/3-U	95% CI	p Value
SCD	1.23	1.14–1.32	<0.0001
Cardiovascular death	1.18	1.14–1.22	<0.0001
Death other than SCD	1.07	1.05–1.10	<0.0001
All-cause mortality	1.09	1.06–1.12	<0.0001

Abbreviations as in Tables 1 and 2.

100 bootstrap samples, the LVEF was retained in 100 samples, the Charlson index in 78, the SSS in 76, hypertension in 72, antiarrhythmic drug therapy in 53, and smoking in 53. The *c*-index of the overall predictive model was stable after correcting for bias (0.72, 95% CI: 0.68 to 0.76).

SCD risk prediction tool. With the beta coefficients from our multivariable Cox model, we constructed a SCD risk prediction tool. In the nomogram, points are apportioned for increasing SCD risk, as reflected by: declining LVEF, increasing SSS, increasing Charlson index as well as antiarrhythmic drug treatment, hypertension, and smoking (Table 5). For example, a patient with an SSS = 10, hypertension, prior history of smoking, antiarrhythmic drug treatment, Charlson index of 4, and an LVEF of 40% would have a point total of 166, which corresponds to a projected 5-year SCD rate of 30%. Projected SCD rates at 3, 5, and 10 years are numerated in Table 6 and shown graphically in Figure 3.

Risk reclassification. To assess the clinical implications of our model, we conducted a risk reclassification analysis (Table 7). According to current guidelines, patients with CAD and an LVEF >35% are not candidates for primary prevention ICD implantation. Therefore, by default, these patients are currently categorized as low-risk in clinical practice. With our SPECT SCD nomogram described in the preceding text, we reclassified the cohort into low-risk (n = 4,839) and high-risk groups (n = 26). High-risk was defined as a 3-year predicted SCD risk ≥10%. The event rate was more than 4-fold greater in the SPECT-nomogram derived high-risk group. Among the 26 high-risk patients identified by the combined SPECT nomogram, 2 sustained an SCD event. Alternatively, the nomogram failed to identify 77 of the 79 SCDs as high-risk. Formal assessments with the NRI and IDI failed to show statistically significant reclassification: NRI = 0.0203 (p = 0.26), and IDI = 0.001 (p = 0.38).

Table 5 SPECT SCD Nomogram

SSS	Points	SSS	Points	Charlson Index	Points	EF	Points
1	2	19	31	1	11	34	57
2	3	20	33	2	22	36	52
3	5	21	34	3	33	38	48
4	7	22	36	4	44	40	43
5	8	23	37	5	56	42	38
6	10	24	39	6	67	44	33
7	11	25	41	7	78	46	29
8	13	26	42	8	89	48	24
9	15	27	44	9	100	50	19
10	16	28	46			52	14
11	18	29	47			54	10
12	20	30	49			56	5
13	21	31	50				
14	23	32	52				
15	24	33	54				
16	26	34	55			Antiarrhythmic	28
17	28	35	57			Hypertension	21
18	29	36	59			Smoking	14

SPECT = single-photon emission computed tomography; SSS = summed stress score; other abbreviations as in Table 1.

Table 6 SCD Rates Across SPECT Nomogram Scores

3-Yr SCD Rate		5-Yr SCD Rate		10-Yr SCD Rate	
Total Points	Risk of SCD	Total Points	Risk of SCD	Total Points	Risk of SCD
137	0.10	119	0.10	94	0.10
144	0.12	136	0.15	111	0.15
151	0.14	148	0.20	123	0.20
157	0.16	158	0.25	133	0.25
162	0.18	167	0.30	142	0.30
166	0.20	174	0.35	149	0.35
171	0.22	181	0.40	156	0.40
174	0.24	187	0.45	162	0.45
178	0.26			168	0.50
181	0.28			173	0.55
185	0.30			179	0.60
188	0.32			184	0.65
191	0.34			189	0.70
194	0.36				

Abbreviations as in Tables 1 and 2.

Discussion

There are 3 important findings from our analysis. First, among patients with CAD and LVEF >35%, stress MPI defects were associated with an increased risk of SCD. Second, MPI added incremental prognostic information to the clinical history and LVEF for the prediction of SCD. Finally, we constructed a risk prediction tool that uses LVEF, stress SPECT MPI results, and clinical risk factors to identify patients with an LVEF >35% at high risk of SCD.

Most SCD events occur in patients with LVEF >35% (22). Previously, we have shown that abnormal myocardial perfusion is associated with SCD and provides incremental prognostic information beyond the LVEF (23). In the current study, we examined the association between MPI and SCD in 4,865 patients with angiographically confirmed CAD and LVEF >35%. In this cohort, after adjustment for baseline characteristics, including coronary revascularization and beta-blocker therapy, the SSS (a global index of total extent and severity of perfusion abnormality) was associated with an increase in the hazard of SCD. Patients with an SSS <8 had a lower incidence of SCD (log rank p < 0.0001). Interestingly, the SRS and SDS were not independently associated with an increased hazard of SCD, suggesting that in this mostly preserved LVEF population, the presence of both "myocardial scar" and ischemia was a more potent driver of sudden death risk than reversible ischemia or scar alone. Ischemia is a well-recognized risk factor for both recurrent ventricular arrhythmias and SCD (24,25). The 1 randomized controlled trial of ICD therapy in patients who were newly revascularized failed to demonstrate a mortality benefit, again illustrating the prominence of ischemia in the pathophysiology of SCD (26). By contrast, hibernating myocardium (which can manifest as a

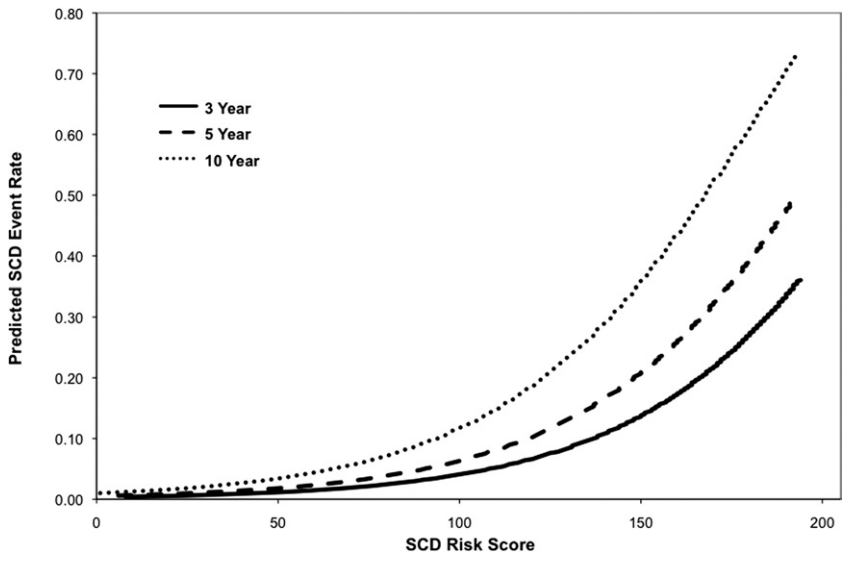

Figure 3 Projected SCD Rates Across SPECT Nomogram Scores

A multivariable Cox model was used to generate a sudden cardiac death (SCD) nomogram. In the nomogram, points are apportioned for increasing SCD risk, as reflected by: declining left ventricular ejection fraction, increasing summed stress score, increasing Charlson index, as well as hypertension and smoking. The projected SCD rates at 3, 5, and 10 years according to the nomogram are illustrated here.

resting perfusion defect) is also a prominent risk substrate for arrhythmogenesis and sudden death (27,28). Further studies are needed to clarify the relative contribution of ischemia, scar, and even hibernating myocardium to SCD risk.

Prior reports have examined factors associated with SCD in patients with CAD and preserved LV function. Al-Khatib et al. (29) examined SCD events in nearly 2,000 patients with diastolic heart failure (LVEF >50%) and found that diabetes, mitral regurgitation, NYHA functional classification, prior myocardial infarction, and CAD severity were associated with an increased risk of SCD. Although their analysis was restricted to patients with an LVEF >50%, their cohort was composed entirely of patients with symptomatic heart failure. In this analysis, where only 16% of the patients had a diagnosis of heart failure, the Charlson comorbidity index, hypertension, antiarrhythmic drug therapy, and smoking were independently associated with the occurrence of SCD.

Table 7 3-Year Risks for SCD as Predicted by Models That Do and Do Not Include Resting Myocardial Perfusion Data

Risk Scheme 2 (SPECT Nomogram) Frequency	Risk Scheme 1 (Current Clinical Practice) Low Risk (LVEF >35%)	High Risk (LVEF ≤35%)	Total
Subjects who experience SCD			
<10%	77	0	77
≥10%	2	0	2
Total	79	0	79
Subjects who do not experience SCD			
<10%	4,762	0	4,762
≥10%	24	0	24
Total	4,786	0	4,786

LVEF = left ventricular ejection fraction; SCD = sudden cardiac death; SPECT = single-photon emission computed tomography.

Prediction of SCD remains challenging, especially among patients with LVEF >35%. Previously, investigators from the PEACE (Prevention of Events with Angiotensin Converting Enzyme Inhibition) trial examined factors associated with SCD in 8,290 patients with CAD and LVEF >40% (30). The PEACE investigators identified current angina, LVEF <50% (vs. ≥50%), diuretic use, and digitalis therapy as factors independently associated with SCD. Our analysis identified LVEF but not angina as a predictor of SCD. Additionally, the PEACE investigators constructed a risk prediction model that could identify patients with a 2.2%/year risk of SCD. With a similar population we constructed a nomogram with clinical factors, LV function, and extent of perfusion abnormality by stress SPECT MPI. With this nomogram, 3-year SCD projections range between 10% and 36% (Table 6). To put this in perspective, the SCD event rate in the MADIT II (Multicenter Automatic Defibrillator Implantation Trial) was 11% at 2 years and 18% at 3 years (31). Therefore, our SPECT nomogram identifies patients with a projected risk of SCD similar to randomized trial populations shown to benefit from ICD insertion.

Although few patients with an LVEF >35% have a high-risk profile, they still outnumber the low-LVEF SCDs in epidemiologic studies, owing to the significantly larger "denominator" of patients with LVEF >35% (32). Although our model only identifies a small fraction of LVEF >35% patients at sufficiently high risk to merit possible interventions to

prevent SCD, given the overall prevalence of CAD with EF >35%, our results have significant clinical implications.

When compared with a model based upon clinical factors and LVEF, the model incorporating SPECT stress perfusion data provided incremental prognostic information as reflected by the improvement in the global chi-square. Although receiver-operator characteristics and *c*-indexes should be viewed cautiously in the setting of risk prediction models (as opposed to diagnostic testing) (33), the *c*-index for our model (0.728) exceeds the discriminatory accuracy of widely used risk stratification tools, including the Thrombolysis In Myocardial Infarction risk score for mortality/death/myocardial infarction in non–ST-segment elevation acute coronary syndromes (*c*-index = 0.63) (34) and the CHADS2 score (*c*-index = 0.58) (35) for the prediction of stroke in patients with nonvalvular atrial fibrillation.

Recently, risk reclassification tables have been identified as a more intuitive and clinically useful way to ascertain the risk stratification properties of a model (36). When we examined the risk stratification of our population with conventional criteria versus our combined nomogram, we found that only 0.5% of the cohort was identified as "high risk." However, if these patients were treated with ICD therapy the number needed to prevent 1 sudden death would have been approximately 13, a figure consistent with prior randomized trials of ICD therapy for low-LVEF populations (e.g., 17 in MADIT II) (3). By contrast, the nomogram failed to identify 77 of the 79 patients who experienced SCD.

Formal assessment of our nomogram with the NRI and IDI failed to show statistically meaningful risk reclassification. One potential limitation of risk reclassification analysis is the dependence on the categories of risk used in the model. This was further complicated in our analysis, because our model only addressed increased risk (e.g., moving from low risk to high risk). Finally, although our nomogram was designed to be applied to a population with a range of LVEF >35%, most of the patients in this study had an LVEF >50%. Therefore, selection of different risk thresholds or the application of our model in a population with greater LV dysfunction (e.g., median LVEF 40% to 45%) might have yielded different results.

Finally, we would like to emphasize that we are not advocating that SPECT MPI serve as a de novo, stand-alone screening tool. However, in patients who have SPECT MPI performed, attention should be paid to those patients with perfusion characteristics associated with a high risk of SCD. Moving forward, optimal risk stratification will likely employ multiple risk markers, including LV function, myocardial perfusion, genomics, and markers of autonomic dysfunction.

Study limitations. The main limitations of this study are the observational nature of the analysis and selection bias. Therefore, our results must be viewed as hypothesis-generating only. However, the association between the SPECT perfusion defects and SCD remained significant after extensive adjustment for clinical covariates, severity of CAD, and LV function. Although we adjusted for pharmacotherapy, including beta-blockade and antiarrhythmic drugs at baseline, we could not account for changes in pharmacotherapy over time. In addition, clinical characteristics and SPECT perfusion data were collected prospectively, in consecutive patients, as part of routine clinical care, thus limiting sampling and diagnostic bias. Another limitation is that, despite quantification of LV function, LVEF determination was not uniform and represented several imaging modalities, including angiography, SPECT, and echocardiography. Nonetheless, there was no association between the source of LVEF determination and SCD in adjusted analysis ($p = 0.15$).

Although cause of death was adjudicated with standard, validated criteria, we cannot exclude the possibility of misclassification bias, which could weaken the strength of the association between prognostic variables and SCD. The list of candidate variables included many known risk factors for SCD; however, other variables known to be associated with SCD were unavailable, including electrocardiography data (e.g., QT interval) and heart rate variability. Entry into the cohort required angiography and >70% stenosis in at least 1 vessel. As such, the results cannot be directly applied to all patients having SPECT studies. Patients who are referred for angiography afterward or in conjunction with SPECT examination typically represent a higher-risk population. Although our predictive model was stable in bootstrap analysis, it should be viewed with caution, because it has a modest *c*-index and has not yet been validated in an external CAD population. Model-building procedures always involve the possibility of overfitting or underfitting without external validation. Despite these limitations, given the large number of patients, the wide range of CAD severity in this cohort, the prospective data collection, and the strict definition and adjudication of SCD, the results are not likely to be spurious.

Conclusions

Among patients with CAD and preserved LV function, SPECT MPI defects are associated with an increased risk of SCD. SPECT perfusion imaging adds incremental prognostic information to the clinical history for the prediction of SCD. Further validation of these findings and prospective studies should address the role of SPECT perfusion imaging for the risk stratification of SCD in patients with CAD and LVEF >35%.

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Key Words: coronary artery disease ■ risk stratification ■ single-photon emission computed tomography ■ sudden cardiac death.